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Final Report
"Effects of Deep Brain Stimulation on Sequence Motor Learning in Parkinson's disease"
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The primary goal of this project was to determine the differential effects of deep brain stimulation (DBS) in the subthalamic nuclei (STN) or internal segment of the globus pallidus (GPi) on sequence motor learning in advanced Parkinson's patients. It was hypothesized that prior to the DBS procedure PD patients will exhibit decreased levels sequence motor learning relative to a group of healthy peers. Furthermore, it was hypothesized that effective DBS will enhance motor learning capabilities.

A sequential motor learning paradigm, modeled after that described by Ghilardi and colleagues (2000), was used to assess motor learning in two groups of PD patients and a group of healthy controls. In this task participants perform center-out movements from a "home" position to targets according to a predetermined presentation of the sequence elements. Since we were testing patients on more than one occasion considerable effort was put forth to make sure at each testing session the sequences that the patient performed was unique. The presentation of unique sequence elements via a computer program that we wrote expands our ability to extend this paradigm to address other motor learning\performance issues. All movements were performed on a WACOM digitizing tablet, thus allowing for the calculation of movement kinematics and kinetics.

Over the past 12 months we have collected data from 11 advanced PD patients (total of 44 testing sessions) with DBS and 10 healthy control subjects (a total of 20 testing sessions). The first month of this project was spent getting personnel in place and developing our data collection and analyses techniques. The programming requirements have been great as there is no commercially available software that can be used for data collection. Therefore, we have written customized software for the presentation of sequences, collection and analysis of participants' movements during the task.

The initial phase of this project was to compare motor learning capabilities of advanced PD patients to healthy controls. The unique aspect of this study was that the PD patients were all scheduled to have the DBS surgical procedure within two months of data collection. It was hypothesized that PD patients would exhibit lower levels of motor learning than control subjects. The primary outcome variables were: number of sequences performed before error, time to perform each segment within each sequence, time and distance in the primary submovement (primary submovement is a measure of feedforward or programmed control) and overall movement time. The results supported our hypothesis as PD patients successfully performed fewer movement sequences during the learning phase compared to controls. Additionally, PD patients performed movement segments and total movements significantly slower than controls. The submovement analysis revealed that PD patients had shorter primary sub-movements, both in time and movement amplitude, compared to controls. Shorter primary sub-movements suggest that PD patients are using more of a feedback type of control as they appear to need more time and distance in which to make corrections to their movement patterns. This finding coupled with our earlier work regarding force control deficits of PD patients during bimanual

dexterous actions (Alberts et al., 1998) suggests that PD patients have difficulty accurately and precisely controlling forces used in the production of movement.

Previously, we have shown that DBS improves force control and grasping force coupling during the production of a bimanual dexterous activity (Alberts et al., 2003). Improved force control with DBS led to the generation of the hypothesis that inability to accurately control force may be the cause of impaired motor learning in PD patients. The second portion of this study examined the question whether DBS would improve motor learning levels in PD patients. Data were collected from the same advanced PD patients who had participated in the earlier motor learning study. These patients had undergone the DBS surgery six months prior to the second data collection period. All of the PD patients who underwent DBS surgery did show a favorable clinical response (~25-40% improvement on UPDRS motor scores), though there was no significant difference or trend for GPi or STN elicit a superior response.

Results from the second data collection session when PD patients were "on-DBS and off meds" indicated that DBS did improve motor learning abilities in seven of the 10 PD patients. The most dramatic improvement, in general, for these patients was an improvement in the kinematics during the performance of each stroke within a sequence. While the number of sequences successfully achieved did increase slightly on average; there were not any significant differences between the number of correct sequences from pre- to post-DBS surgery. Considering the relatively low number of PD patients that were included in the sample it is not unexpected to have non-significant results. However, we preformed detailed kinematic analyses on the movements that PD patients made during successful sequences. These data provided confirmatory evidence for our hypothesis that DBS does improve the force control capabilities of PD patients, which in turn, allows them to use more of a programmed or feedforward mode of movement control. Kinematic analyses indicated that while on DBS PD patients were able to extend the time and distance spent in the primary sub-movement of the movement. These data suggest that with improved force control patients could program their limb movement to terminate closer to the target initially that then required them to make fewer secondary corrective actions to actually reach the target. Hence, DBS appears to be allowing PD patients to use a completely different control strategy when performing target directed reaching/pointing.

Analyses of the data collected from the "on-DBS and on-meds" condition indicated that there was no additive effect of medication on movement performance. Again it is important to note that this study was a pilot study and therefore the sample size was not sufficient to detect such a difference between conditions. In general, overall performance in the two post-DBS conditions were similar in terms of movement time, sequences learned and primary submovement time and amplitude. There were no statistically significant differences between patients with GPi or STN stimulation, most likely due to the relatively small sample size. However, there was a slight trend that GPi patients improved more than STN patients. The two patients with the greatest improvement in primary submovement distance were GPi patients. While DBS did have positive effects on movement performance and motor learning levels, patients did not reach learning and performance levels of control subjects. It is possible that additional practice trials or using a different type of motor learning task that is more dependent on the control of forces (e.g. a grip force tracking task) may elicit greater improvements in PD performance as the current task did have a relatively large cognitive component.

In summary, we are extremely pleased with the outcome and progress of this project. The support of the American Parkinson's Disease Association has been valuable in the development of Dr. Alberts' career and Motor Control Laboratory at Georgia Tech. This project has allowed Dr, Alberts to foster collaborations with Dr. Jerrold L. Vitek within the Department of Neurology at Emory University. We envision this project to be the first in a series of studies aimed at understanding the deleterious effects of PD on motor learning. We are currently working on additional analyses and on the re-submission of an NIH R01 grant (Alberts, PI) to systematically determine the effects of PD and DBS on motor performance and learning. The reviewers criticized our lack of motor learning pilot data. With the current data we will be able to address this criticism fully. The primary hypothesis to be tested is that deficits in force control lead to motor learning and performance impairments and that DBS is an effective intervention to improve force control, thus, motor learning and performance should exhibit improvements in PD patients with DBS. Portions of this data were recently presented at the 2003 International Graphonomics Society, Scottsdale, AZ. to submit an abstract of this project for their upcoming conference in November.